دانشگاه علوم پزشکی و خدمات بهداشتی درمانی بوشهر
دانشکده پزشکی

پایان نامه دوره دکترای حرفه ای پزشکی

بررسی تاثیرلتروزول درزنان نابارور مبتلا به سندروم پلی کیستیک تخمدان مقاوم به کلومیفن در مراجعه کنندگان به کلینیک ابوالفضل (ع) از سال ۱۳۸۵ تا ۱۳۸۷

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این طرح با تصویب و حمایت مالی حوزه معاونت پژوهشی دانشگاه علوم پزشکی و خدمات بهداشتی درمانی بوشهر اجرا گردیده است.

شهریورماه ۱۳۹۱

In The Name of GOD

To:

My Dear Father, My Dear Mother
and
My Dear lovely Sister

Those who are my life, love, energy and I will never be so powerful to thank them...

To:

My Dear Wife

For all the things I can not count them…

Thanks to:

Dr. Elham Rahmani
and
Dr. Niloofar Motamed

Those who learn me thinking but not the thoughts.

Dosage Optimization for Letrozole Treatment in Clomiphene-Resistant Patients with Polycystic Ovary Syndrome: A Prospective Interventional Study

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Objective: Dose adjustment for induction of ovulation is one of the most important problem. **Methods:** In a prospective interventional study, 44 clomiphene-resistant infertile patients (113 cycles) were selected from the Abolfazl Infertility Clinic of Bushehr University of Medical Sciences. Letrozole was given orally in a dose of 2.5 mg, 5 mg, and 7.5mg, respectively. If the patient displayed no response, the dosage was increased.

Results: In these patients ovulation occurred in 50 cycles (44.24%), clinical pregnancy rate according to number of cycles was 23.89% (27 of 113 cycles) and according to the number of patients was 61.36% (27 of 44 patients). In the 2.5, 5, and 7.5 groups, follicles occurred in 22.9%, 42.1%, and 85.18% of cycles, and pregnancy rate was 14.58%, 28.94% and, 33.33%, respectively.

***Conclusions*:** It is better to administer Letrozole at a lower dosage to prevent complications and increase the dose based on sonographic results antral follicular count, anti-Mullerian hormone, LH/FSH, and estradiol.

Key words: infertility, letrozole, clomiphene citrate, polycystic ovary syndrome

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Infertility

Infertility is a common condition with important psychologic, economic, demographic, and medical implications. Demand for infertility services has grown substantially even though the prevalence of infertility has been stable. This phenomenon may be due to entry of the "baby boom" generation into the reproductive age group during a period of highly publicized technologic advances, and unparalleled publicity given to fertility issues in the lay press.

Infertility is a unique medical condition because it involves a couple, rather than a single individual. It is defined as failure of a couple to conceive after 12 months of regular intercourse without use of contraception in women less than 35 years of age; and after six months of regular intercourse without use of contraception in women 35 years and older [1]. Some clinicians use the term subfertility to describe this failure to conceive unless the couple has been proven to be sterile.

Fecundability, the probability of achieving a pregnancy in one menstrual cycle, is a more accurate descriptor because it recognizes varying degrees of infertility.

Normal Fertility: The concept of fecundability has proven useful for establishing normal parameters in studies of fertility potential:

- A study examined the number of months to conception in 5574 normal women who had unprotected intercourse and who became pregnant between 1946 and 1956 [2]. Eighty-five percent of the women conceived within 12

months. Fecundability was 0.25 in the first three months of observation, and then decreased to 0.15 during the next nine months of observation.

- Another study of 200 healthy couples who desired pregnancy also noted that fecundability declined from 0.25 in the first three months to 0.11 in the next nine months of observation [3]. Eighty-two percent of the couples conceived within 12 months.
- A study conducted in China reported that 518 newly married textile workers aged 20 to 34 years who intended to conceive did so at a rate of about 50 percent within two cycles and 88 percent within six months [4]. Monthly fecundity ranged from 0.30 to 0.35.
- A large prospective European study investigated 346 users of natural family planning methods who were trying to achieve conception [5]. The estimated cumulative probabilities of conception for the total group at 1, 3, 6, and 12 months were 38, 68, 81, and 92 percent, respectively. The authors postulated that after six months, 50 percent of the remaining couples were subfertile or infertile.

While these studies demonstrate that the large majority (80 to 90 percent) of apparently normal couples will conceive within the first year of attempted conception, they also show that the fecundability of the cohort decreases over time and with increasing age of the female partner. Thus, the possibility of infertility may be suspected after only six months of unprotected intercourse without conception. Patients who have not achieved pregnancy after 12 months have even lower fecundability. Five to 15 percent of apparently normal couples will conceive in the second 12 months of attempted conception so that after 24 months of trying to become pregnant, 95 percent of couples will have conceived.

Several authorities have proposed a system of prognostic grading in conjunction with statements describing the couple's fertility history and diagnosis in order to reduce confusing terminology and to facilitate an appropriate treatment plan [6]. This system has not yet been widely accepted. In general, women who are under age 30, who have a less than two-year history of infertility, who have had a previous pregnancy, and who do not have tubal disease, anovulation, partners with male factor infertility, or endometriosis, have the best prognosis for treatment-independent conception [7].

Prevalence of infertility: The National Survey of Family Growth interviewed 15,303 married women aged 15 to 44 to estimate the prevalence of infertility in the United States [8]. Married women were considered infertile if they reported they had not conceived over the past 12 months and were sexually active and not using contraception or surgically sterilized [8]. From 1982 to 2002, the percentage of married women meeting these criteria for infertility fell from 8.5 to 7.4 percent.

In contrast, the estimated percent of married women with impaired fecundity increased from 11 percent in 1982 to 15 percent in 2002 [9]. Impaired fecundity was defined as a 36-month interval of unprotected sexual activity without conception or the woman's perception that it was physically impossible or difficult for her to conceive or her husband to father a child (does not include surgically sterile individuals).

The reasons for these discordant trends cannot be fully explained. However, it is clear that many women seek medical advice and intervention to help them become pregnant. The National Survey of Family Growth reported that 1.2 million women (2 percent of reproductive aged women) had one or more visits with a health care provider for this indication in 2002 and 10 percent had received infertility services at some time in their lives [9].

Race and ethnicity: It is not known whether fecundity varies among racial and ethnic groups when adjusted for confounders.

The National Survey of Family Growth found that married black women had about twice the odds of infertility as married white women, after adjustment for education, income, and self-reported history of pelvic inflammatory disease [8]. Others have shown that this disparity cannot be explained by differences in common risk factors for infertility, such as smoking, obesity, fibroids, or ovarian volume [10].

This report also noted that the proportion of US Hispanic women reporting infertility has remained stable and white women have experienced a decline. There are no data on US Asian women.

Causes of infertility: The World Health Organization (WHO) task force on Diagnosis and Treatment of Infertility performed a study of 8500 infertile couples and utilized standard diagnostic criteria to determine the medical conditions contributing to infertility [11]. In developed countries, female factor infertility was reported in 37 percent of infertile couples, male factor infertility in 8 percent, and both male and female factor infertility in 35 percent. Five percent of couples had unexplained infertility and 15 percent became pregnant during the study. This study illustrates that infertility should not be assumed to result primarily from disorders in the female partner.

Some causes of infertility are easily identifiable, such as azoospermia (no sperm cells in the ejaculate), longstanding amenorrhea, or bilateral tubal obstruction. However, the situation is less clear in most couples: the sperm may be reduced in number, but are not absent; there may be oligomenorrhea with some ovulatory cycles; the woman may have partial tubal obstruction; or a menstrual history may

suggest intermittent ovulation. It is often difficult to weigh or prioritize these findings when counseling infertile couples or planning treatment programs.

Adding to the complexity of the situation, there are few data regarding the predictive validity of these tests despite their widespread use. Thus, short of the absolute infertility factors mentioned (eg, azoospermia or bilateral tubal obstruction), an abnormal test result cannot be said to be the cause of infertility in a particular couple.

The uncertain causal relationship between an abnormality on infertility testing and the actual cause of infertility makes it difficult to estimate the relative frequency of the causes of infertility. Nevertheless, it is instructive to estimate the frequency with which various factors are found in association with infertility as a rough proxy for their relative importance. One population-based study reported the following results [12]:

- Male factor (hypogonadism, post-testicular defects, seminiferous tubule dysfunction) — 26 percent
- Ovulatory dysfunction — 21 percent
- Tubal damage — 14 percent
- Endometriosis — 6 percent
- Coital problems — 6 percent
- Cervical factor — 3 percent
- Unexplained — 28 percent

The frequency of these factors in infertility is similar whether infertility is primary or secondary, and has not changed significantly over the past 25 years in developed countries [13].